UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/211,315	12/14/98	BOYLE W	A-451-G

HM12/0608

US PATENT OPERATIONS/RBW
DEPT 430 M/S 27-4-A
AMGEN INC
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1645	8

DATE MAILED: 06/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/211,315	Boyle
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1645

☒ Responsive to communication(s) filed on *3-25-99*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *37-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit of U.S. Patent application SN 09/211,315 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Art Unit 1645.

Priority

2. If applicant desires priority under 35 U.S.C. based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Drawings

3. The drawings submitted with this application were declared informal by applicant. Accordingly they have not been reviewed by a draftsperson at this time. When formal drawings

are submitted, the draftsperson will perform a review. Direct any inquires concerning drawing review to the Drawing Review Branch (703) 305-8404.

Election/Restriction

4. Applicant's election without traverse of the inventions of Group VII in Paper No. 6 filed 3-25-1999 is acknowledged. Accordingly, GroupVI will be examined with Group VII as they are linked. Pursuant to the amendment, claims 1-36 have been canceled, claims 37-49 are pending.

Claim Objections

5. Claim 49 is objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. . See MPEP § 608.01(c). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

6. Claims 37-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Claims 37-49 are drawn to a method of treating bone disease in a mammal comprising administering a modulator of an osteoprotegerin binding protein (OPG-bp). The following

factors are used to show that there is insufficient enabling written disclosure to allow one of skill in the art to make and or use the claimed invention. (1) The breadth of the claims, (2) the unpredictability in the art (3) the method of treatment (4) the lack of skill in the art (5) the absence of treatment examples (6) the quantity of necessary experimentation and (7) a lack of such direction or guidance of the specification. The limitations of each claim will be addressed.

Claim 37, as recited above, encompass modulators, for instance, osteoprotegerin binding protein agonists, antagonists, and molecules which bind to or affect any function of OPG-bp, such as the ability to bind OPG polypeptides or regulate osteoclast maturation, see specification, page 22, lines 10-29. Included within this scope is, for instance, antisense therapy with DNA nucleic acids specific to OPG-bp mRNA. Antisense therapy is an unpredictable art which relies on many factors including the route of administration, the copy number of the antisense molecule within the cell to be targeted, the copy number of the OPG-bp mRNA within the host cell, the activity of cellular enzymes which degrade RNA-DNA templates, the length of the antisense molecule, the specificity of the antisense molecule to OPG-bp mRNA, toxicity to the host cell and the relative number of targeted host cells. For review see Crooke et al, An overview of progress in antisense therapeutics, Antisense & Nucleic Acid Drug Development, 8:115-122, 1998

Claim 38 is drawn to the method of claim 37 wherein the modulator is an antibody or fragment thereof which binds OPG-bp. Claims 39-46 are each drawn to the methods of claim 38 but differ in antibody compositions. Claim 39 is a monoclonal antibody, claim 40 is a

recombinant antibody, claim 41 is a chimeric or CDR-grafted antibody, claim 42 is a human antibody, claim 43 is an antibody prepared by immunization of a transgenic animal capable of producing human antibodies, claim 44 is an antibody that binds to an extracellular domain, claim 45 is an antibody that binds to the BB' loop, and claim 46 is an antibody that binds the EF loop. OPG-bp may be soluble or membrane associated. The properties of OPG and OPG-bp are unknown, however soluble and membrane associated OPG-bp most likely differ in structure and function. For instance, OPG-bp may exhibit signal transduction properties when membrane bound whereas soluble OPG-bp may not. With respect to these differences, different properties are most likely associated with antibodies of different epitope specificity. For instance, an antibody binding an extracellular domain could simply detect OPG-bp without altering function. Antibodies can bind to transmit signals, or alternatively can bind to block intracellular signals. Even amongst highly homologous epitopes the effects or lack thereof amongst specific antibodies is unpredictable. In addition, within the context of the host, antibodies with different Fc portions possess different functional abilities to be recognized by host cells. For each antibody, one of skill in the art would require inventive experimentation to deduce the properties associated with binding to each epitope of OPG-bp. Furthermore, these factors must be investigated with respect to a method of treatment relating to OPG-bp.

Claim 47 is drawn to the method of treatment of claim 38 wherein the antibody or fragment further comprises a composition comprising a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant. The specifics of this composition

are not specified and the properties of such compositions differ. For instance a robust immune response may be generated with a protein in a composition containing Freund's adjuvant and a preservative whereas a more mild system for delivery may be the pharmaceutical diluent water. The ideal composition would depend on the desired method of treatment and the specific disease.

Claim 48 is drawn to any of claims 37-47 further comprising administering a bone morphogenic factor selected from the group consisting of BMP-1 to BMP-12, transforming growth factor-β (TGF-β), a TGF-β family member, a fibroblast growth factor selected from the group consisting of FGF-1 to FGF-10, an interleukin-1 inhibitor, a TNFα inhibitor, parathyroid hormone, an E series prostaglandin, a bisphosphonate, or a bone-enhancing mineral. Bone diseases are complex disorders which manifest themselves in overproduction or degeneration in bone density. Osteoblasts promote bone growth whereas osteoclasts resorb bone material. Homeostasis in this system is regulated by growth activating and inhibiting factors which act on each cell individually as well as cumulatively. For example, three known pathways influence osteoclast differentiation including; vitamin D receptor mediated signals, protein kinase A mediated signals and gp130 mediated signals. Amongst many modulators in osteoclast differentiation are parathyroid hormone, prostaglandin E_2, and cytokines including IL-1, IL-6, IL-11 and M-CSF, reviewed in for example Suda T, Bone, 17(2):87S-91S, 1995. Alternatively osteoblast proliferation and signaling are induced by bone morphogenetic proteins, TGF-β, FGF and cytokines such as IL-1 and TNF-α. Clearly, osteoclastogenic and osteoblastogenic signals

cross react and only balance amongst such signals maintains healthy bone homeostasis. Production of osteoprotegerin is associated with osteoblastic bone deposition whereas production of OPG-bp is associated with osteoclastic bone resorption. However, depending on the disease state, it is likely that different perturbations must be corrected so as to return to normal function. For example, IL-1 induces osteoclast formation, but IL-1 also induces the production of osteoprotegrin in osteoblastic cells. The balance of IL-1, in conditions such as rheumatoid arthritis, may be critical in achieving bone homeostasis regardless of production of osteprotegerin or OPG-bp.

Claim 49 is drawn to any of claims 37-48 wherein the bone disease is selected from the group consisting of osteoporosis, osteomyelitis, hypercalcemia, osteopenia brought on by surgery or steroid administration, Paget's disease, osteonecrosis, bone loss due to rheumatoid arthritis, periodontal bone loss, osteopenia due to immobilization, prosthetic loosening and osteolytic metastasis. The treatment of any disease relies to some extent in counteracting the causative agent. In some instances a treatment may be beneficial without counteracting the causative agent. In other instances a treatment could exacerbate a disease depending on its mechanism. In the instance of osteomyelitis, the causative agent is pathogenic bacteria. In the instance of Paget's disease, no known cause has been identified but hypotheses include genetic mutations or viral infection. These diseases for example may derive little benefit from approaches targeting OPG or OPG-bp, especially if overriding signals could counteract the measures taken to produce for example OPG-bp. Given the complexity of human disorders and a multiplicity of factors

affecting osteoblastic and osteoclastic activity, it is impossible to predict whether a specific antibody will be functional in any disease. For example, in an osteopetrotic *op/op* mouse a frameshift mutation in M-CSF was determined and treatment with recombinant M-CSF was effective. It is uncertain what benefit an *op/op* mouse could derive from treatment with an OPG-bp antibody with or without M-CSF.

For the reasons discussed above, claims 37-49, drawn to a method of treatment with any modulator or antibody to OPG-bp, would require extensive inventive experimentation, which lacks further direction in the specification and is considered undue. In addition, no working examples of OPG-bp antisense or antibody therapy have been shown *in vivo* which supports a benefit of any such treatment. The function of OPG-bp and OPG interaction remain to be discovered although interaction is believed to be involved in differentiation and activation of osteoclasts. In short there is no known evidence to support the benefit or treatment of a bone disease with a modulator or antibody to OPG-bp.

Status of Claims

8. No claims are allowed.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Sharon L. Turner, Ph.D.
May 27, 1999

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600